CLASSIFICATION ~~CONFIDENTIAL~~ C

CENTRAL INTELLIGENCE AGENCY
INFORMATION FROM
FOREIGN DOCUMENTS OR RADIO BROADCASTS

REPORT [redacted] STAT

CD NO.

COUNTRY USSR

DATE OF INFORMATION 1952

SUBJECT Scientific - Medicine, autoallergy, toxicology, blood transfusion

HOW PUBLISHED Bimonthly periodical

DATE DIST. 2 JUNE 1954

WHERE PUBLISHED Moscow

NO. OF PAGES 5 STAT

DATE PUBLISHED May-Jun 1952

LANGUAGE Russian

SUPPLEMENT TO REPORT NO.

THIS IS UNEVALUATED INFORMATION

SOURCE Uspekhi Sovremennoy Biologii, Vol XXXIII, No 3, pp 405-430

USSR WORK ON AUTOALLERGIC REACTIONS AND THEIR SIGNIFICANCE IN PATHOLOGY

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It is erroneous to consider the irritation produced by antigens apart from that produced by nonantigenic irritants and to assume the former type irritation is fundamentally distinct from the latter. A. D. Ado (1951) has shown that the science of allergy must be revised in that respect. A nonspecific and nonantigenic irritant may denature the proteins of the body. The denatured proteins may in turn act on the receptors of the organism, producing a type of allergy which is known as autoallergy. I. P. Petrov and L. G. Begomolova (1938) found that sensitization of dogs produced by an aseptic turpentine-caused inflammation results in disturbances of blood circulation and of respiration following injection of hemolyzed canine blood.

The published research on cytolysins gives many instances of the formation of autocytolysins.

No experimental work aiming directly at the production of autohemolysins has been published. However, the fact that serum exerts an autolytic effect in human pathology has been established by clinical observations. The fact that the contents of artificial hematomas act as autoantigens in rams was discovered by P. F. Zdrodovskiy (1950) with the aid of a modified Abderhalden reaction.

A considerable amount of information on autoagglutinins has been published. In autoagglutination, erythrocytes are made to adhere to each other by the serum of the autogenous blood from which they are derived. It has been established that autoagglutination occurs in a number of diseases: cirrhosis of the liver (A. I. Torgunova, 1922; Ye. M. Tareyev and M. V. Dorogova, 1950), anemias, diseases produced by trypanosomes, hemolytic jaundice, pernicious anemia of pregnancy (A. V. Demidova, 1928), Raynaud's disease (Ye. M. Tareyev and Dorogova, 1950),

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and virus pneumonia. Occasionally, autoagglutination was observed in clinically healthy persons (K. L. Rubasheva, 1927; G. S. Ivakhnenko, 1937; N. I. Blinov, 1940) and in pregnant women (I. G. Kartashevskiy, 1937). As a rule, autoagglutination is encountered only in pathological cases. However, autoagglutinins which have a low-temperature range of activity, i.e., they are active below plus 8° C are present in the bodies of 94% of healthy human beings, according to the data of Tareyev and Dorogova.

Views on the nature of autoagglutination differ. The interrelationships between autoagglutination, agglutination at low temperatures, and panagglutination are also not quite clear. Some authors deny that the autoagglutination reaction is specific (A. Bagdasarov and P. Sel'tsovskiy, 1939; N. I. Blinov, 1940). Ye. I. Freyfel'd (1947) assumes that low-temperature agglutination is basically different from autoagglutination. Autoagglutination occurs as a result of a pathological decomposition of erythrocytes. Although the nature of autoagglutination is not definitely known as yet, there are good reasons to regard this reaction a immunological.

A. I. Togunova (1922), B. Shklyar (1934 and 1948), and F. A. Mikhaylov (1948) have proved definitely that autoagglutinins must be regarded as immunoagglutinins. According to the results obtained by these investigators, the nonspecific nature of autoagglutination is only apparent. Togunova has described a case of hypertrophic cirrhosis of the liver, in connection with which she observed pronounced autoagglutination of erythrocytes. The agglutination took place immediately after transfer of the blood into the mixer, but disappeared when the temperature in the mixer reached a level corresponding to body temperature. Togunova also established that in the case of cirrhosis observed by her, the patient's serum agglutinated the patient's own erythrocytes in a much higher dilution than the erythrocytes of a healthy person. This must be regarded as an indication that the reaction was specific and that antibodies were formed.

Shklyar also demonstrated that autoagglutination must be regarded as an immunological reaction, and furthermore showed that liquids which do not contain agglutinins (e.g., a physiological salt solution) are capable of agglutinating the erythrocytes, i.e., that the erythrocytes are already preagglutinated. Mikhaylov proved in his work that, in the blood of some patients, antibodies against a patient's own erythrocytes are formed, and that the agglutinating capacity of the serum could be eliminated by interacting the serum with the erythrocytes.

The papers which have been cited show that the antigenic properties of erythrocytes arise as a result of damage to the erythrocytes. The erythrocytes also must be damaged (hemolyzed) in order that isohemolysins be formed in a sufficient quantity to produce ictus immunisatoricus on parenteral administration of a large dose. Autohemolysins are also formed when erythrocytes are damaged; they were obtained by the action of phenylhydrazine on erythrocytes. One may assume that the antigenic properties of erythrocytes in autoagglutination and autohemolysis are due to denaturation of the erythrocytes produced by chilling of the body (in paroxysmal hemoglobinuria) or by the action of products of disturbed metabolism in various diseases.

Of great importance are investigations which indicate that autoantigens are of importance in the complex process of immunization due to the presence of a focus of inflammation or the existence of a toxicoinfectious affection, i.e., under conditions when autogenous tissue forms an important component of the antigen. Data which show that tissues infected with tuberculosis exert an antigenic effect on the patient have been obtained by a group of USSR investigators. The assumption was made that the patient's own tissue which has acquired antigenic properties plays an important part in the pathogenesis of tuberculosis.

The work of Petrov and Bogomolova cited above illustrates the antigenic effect of tissue from a focus of inflammation that does not contain heterogenic antigens.

F. Shuts (1936) investigated the effect of heat injuries on the antigenic action of tissues. He discovered that injection, into an animal which has suffered a skin burn, of an extract from its burned skin helps produce death of the animal. Death is accompanied by modification of internal organs which are typical for lethal skin burns. When extracts from burned skin were administered to animals which had never suffered a burn, no reaction resulted. Reactions to subcataneous injection of the extract did arise when the animals (guinea pigs) had been subjected to one to three burns prior to administration of the extract. The substances contained in the extract proved to be species nonspecific.

Depending on the number of burns, increased sensitivity or reduction of local or general sensitivity to burns could be observed. The serum of animals "immunized" to burns was found to have the property of preventing the death of animals subjected to otherwise lethal burns and of alleviating the skin reaction.

Kanykevich (1939), who clinically investigated immunobiological reactions produced by burns, found that complement was absent in 33.5% of the patients suffering from burns, had a titer of 0.1-0.2 in 30.9% of the patients, and had a titer of 0.01-0.04 in 33.6% of the patients. At the same time, the agglutination reaction with the bacterial emulsion prepared from the microflora of the burn blisters was negative in 96.7% of the cases.

Numerous attempts to isolate specific antigens of tumor tissues have been unsuccessful. Only recently, investigations by L. A. Zil'ber (1948) established that antigens which are absent in normal tissues are present in tumor tissue. Zil'ber also discovered the presence of antibodies to the nucleoproteid fractions of tumor proteins in animals which had tumors. Later, Zil'ber (1950) treated guinea pigs with the nucleoproteid fraction of their tumors and desensitized them by administering the nucleoproteid fraction of their body proteins (the nucleoproteid fraction of the tumors contains antigens of two types: tumor proteins and the proteins of the animal's body). When the nucleoproteid fraction of tumor proteins was administered to desensitized guinea pigs, they responded by a strong allergic reaction which often had the characteristics of a full-fledged allergic shock.

Traditionally, serum disease is ascribed solely to the introduction of serum of a heterogenous species. However, numerous references published in USSR literature indicate that serum disease may also occur as a result of administration of homologous serum. V. N. Shamov and Ye. G. Karavanov (1940) stated that anaphylactic reactions occur frequently in blood transfusion. However, in the cases described by them there is no strict delimitation between anaphylactic shock and the posttransfusion shock which resembles it. Sensitization may develop not only to agglutinogens, but also to the serum of the donor. Shamov and Karavanov have observed three instances of such sensitization. Direct proofs of the sensitizing properties of homologous blood have been obtained: sensitization of the skin to blood of the same group could be brought about.

The sensitizing effect of sera apparently results from denaturation, which endows them with the properties of heterogenous sera. G. M. Gurevich and D. A. Kogan (1939) have shown that when blood was taken from the vein of a human subject and injected into the same subject, allergic reactions resulted. Many investigations published by USSR workers show that, notwithstanding the close affinity of autogenous and homologous sera to the organism, these sera still produce reactions which are due to denaturation of the serum proteins.

The possibility of bringing about autosensitization by means of sera has been shown by us (M. Z. Sigal, 1949, 1951) in work done on sheep and rabbits at Ado's laboratory. Sheep sera were subjected to the action of sulfuric acid, repeated freezing and thawing, and irradiation with radium. Rabbit sera were denatured by the action of acetone at low temperatures or by means of sulfuric acid. Experiments showed that repeated subcutaneous administration of autogenous sera treated in this manner produces a local hyperergic inflammation. Intracutaneous injection of autoallergens to autosensitized sheep results in positive skin reactions. Trypan blue which has been introduced intravenously is then resorbed to an increased extent at the foci of the reaction. A necessary condition for the autoallergenic activity of autogenous sera is their denaturation.

We established the peculiar characteristics of autoallergic reactions which distinguish them from heteroanaphylaxis. Thus, the hyperergic inflammation is less strongly pronounced in autoallergic reactions. The "precipitin expression" of sensitization is absent. Nevertheless, the passive transmission of heightened sensitivity is possible in autoallergy. At the same time, the reaction of passive anaphylaxis proceeds according to the protracted anaphylactic shock type.

Experiments were carried out in which the primary toxicity of the denatured sera was eliminated. These experiments demonstrated that the antigenic activity of the sera is preserved in heterogenous administration. The autoallergenic sera, when administered to sensitized animals of another species, produced a typical Arthus-Sakharov phenomenon and led to the formation of precipitins when the titer was high enough. The modifications to which the sera were subjected in our experiments did not result in a loss of their species specificity. We have thus shown the possibility of autosensitization and the significance of the denaturation factor in the autoallergenic activity of the sera. We have also determined the differences between the manifestations of autoallergy and those of heteroallergy and heteroanaphylaxis.

A number of investigations on immunization with colloidal metals can be understood by considering the interaction of these metals with autogenous proteins (Zil'ber, 1948), i,e., the denaturation of body proteins as a result of the action of colloidal metals. Zil'ber and V. V. Frize immunized rabbits with colloidal gold or colloidal iron. After intensive immunization, the sera of the animals precipitated the antigen. V. Chernokhvostov and L. Kats (1929) established that colloidal arsenic trisulfide possesses antigenic properties. Chernokhvostov (1931) also found that it is possible to sensitize rabbits with antimony trisulfide. He showed in experiments that immunization of rabbits by 10-12 injections of antimony trisulfide yielded a serum with a pronounced precipitating capacity. Zil'ber expressed the opinion that the antigenic properties of colloidal metals depend on the capacity of these metals to combine with body proteins.

S. V. Rybinskiy (1935) described a case of instantaneous death after intravenous administration of sodium thiosulfate to a patient suffering from thiosulfate eczema. The exzema apparently was caused by the action of chemicals the patient had come in contact with at a pholographic laboratory. Rybinskiy assumed that death was due to anaphylactic shock, and that the administration of thiosulfate released the anaphylactic shock, because the patient had been gradually sensitized by thiosulfate that penetrated through the eczematous fissures. Rybinskiy expressed the opinion that the sensitization occurred as a result of the interaction of the thiosulfate with the patient's proteins.

In experiments on guinea pigs, the possibility of sensitization with a mixture of sodium thiosulfate and horse serum was shown.

The investigations mentioned above and other work in regard to the influence of various chemical substances and physical agents on the course of immunological reactions show that autogenous protein acts as an intermediate link in bringing about changes of the body's reactivity under the influence of various chemical and physical agents. The modification of autogenous proteins and the direct action of the irritant must be regarded as the causes of changes in the reactivity of the organism. The new immunological state which results implies reactivity of the organism to chemical and physical factors of protein denaturation.

One may further assume that there is participation of autoallergens in para-allergic reactions and that these autoallergens also act as antigens and as agents which release anaphylaxis. In regard to homologous serum, these relationships have been proved by Ado, Petrov, and Bogomolova.

Ado and collaborators (1947) have investigated the capacity of skeletal muscles to combine with water as influenced by the sensitization of the organism with heterogenous protein. They established that reduction of the hydrophilic properties of sensitized muscles in vitro takes place not only under the influence of the antigen (e.g., equine serum), but also under the effect of homologous serum. Ado assumes that in the experiments described there was a para-allergic reaction to the homologous serum which reflected the same changes of reactivity as a genuine allergic reaction. Petrov and Bogomolova were able to demonstrate that dogs sensitized by equine serum exhibited an increased sensitivity to both heterogenous plasma and homologous hemolyzed blood. Repeated introduction of human blood into dogs resulted in an increased sensitivity of the dogs to homologous canine blood, while repeated introduction of homologous hemolyzed blood (i.e., canine blood) brought about increased sensitivity to human blood and plasma.

I and a number of other USSR investigators established (1950) the occurrence of allergic reactions as a result of surgery. In surgical operations, tissue is detached in the region of the wound and becomes denatured. This tissue then acts as an allergenic irritant.

We tested the skin reactions of patients in the postoperational period to intracutaneous introduction of substances taken from the wound region. The reactions to these autoallergenic substances proved to be uncertain. However, local serum reactions to intracutaneous introduction of antireticulocytotoxic serum or of equine serum, which acted as para-allergens, were regularly obtained.

The data listed above indicate the great significance of autosensitization in clinical pathology. One must admit that problems of autoallergy have not yet been adequately investigated. Further research in the field of autoimmunological reactions may disclose important relationships pertaining to the course of pathological processes that are not due to the action of microorganisms. Further research will also undoubtedly clarify problems connected with the participation of autoantigens in toxicoinfectious processes as components of complex antigens.

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